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FINAL REPORT

ISOCHROMAN CHEMISTRY

Submitted 30 June 1955

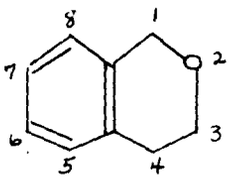
NR 122-013

Contract NONR 06000

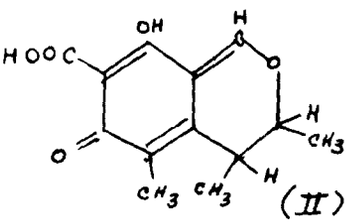
Initiated	25 May 1950
Termination	30 September 1954
Principal Investigator	R. D. Sprenger
Contractor	College of Puget Sound

ISOCHROMAN CHEMISTRY

The project "Isochroman Chemistry" has involved the study of new methods of synthesis and the reactions of isochroman (I) and selectively substituted isochroman.



(I)



(II)

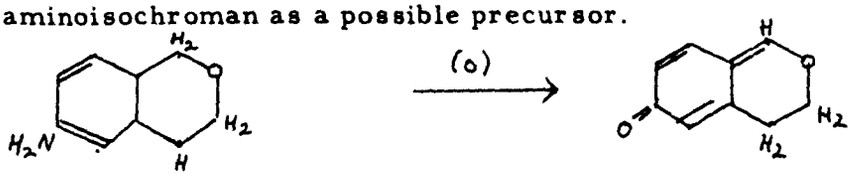
Citrinin (II), an antibiotic mold metabolic product may be considered a substituted and oxidized isochroman and a considerable number of model compounds structurally related to citrinin have been prepared and biologically evaluated.

ACCOMPLISHMENTS AND PRESENT STATUS OF WORK

Two previously unreported methods of synthesis for isochromans have been developed and some thirty substituted isochromans have been prepared and characterized. Of the model compounds of citrinin prepared, some have shown biological activity, but none appears to show sufficient promise for a potential medicinal agent.

At the time of the expiration of the contract, two model compounds, 6,8-dihydroxyisochroman and 1-carboxyisochroman remain to be biologically tested. The structure of one of the bromo substituted isochromans has yet to be determined.

No para-methylene quinoid structures have been realized as yet altho a serious effort has been made to synthesize 6-aminoisochroman as a possible precursor.



Thus far no attempted synthesis has been successful but efforts are continuing with the hopes of studying representative methylene quinoids.

Although a considerable number of interesting avenues of related researches have been uncovered, it is felt that the basic objectives of the Project have been realized.

PERSONNEL

R. D. Sprenger: Principal Investigator Sept. 1950 - Sept. 1954

GRADUATE STUDENTS

W. L. Bean	Sept. 1950 - June 1951
J. L. Wietz	Sept. 1950 - June 1952
Harvey Aft	Sept. 1950 - June 1952
Frank Hayashi	Sept. 1950 - June 1952
Richard L. Rose	Sept. 1952 - June 1954
Richard E. Carlson	Sept. 1952 - June 1954
Donald K. Burns	Feb. 1954 - June 1955

STUDENT ASSISTANT

Philip Funke	June - Aug. 1954

LIST OF REPORTS, MANUSCRIPTS, ETC.

Annual Progress Report	1 Jan 1951 - 31 Dec. 1951
Semi-Annual Progress Report	1 Jan. 1952 - 20 June 1952
Semi-Annual Progress Report	1 July 1952 - 31 Dec. 1952
Annual Progress Report	1 Jan. 1953 - 31 Dec. 1953
Results of Biological Testing	Jan. 1954

"THE OXIDATION OF ISOCHROMAN" by W. L. Bean and R. D. Sprenger. Paper presented at Pacific Northwest Regional meeting of American Chemical Society, Seattle, Washington, June 8, 1951.

GRADUATE THESES

William C. Bean	The Chemistry of Isochroman Master's Thesis - June 1951
Harvey Aft	The Synthesis of Dihydroxy Substituted Isochromans Master's Thesis - June 1952
John J. Wietz	The Synthesis and Characterization of 7 - Carboxy Isochroman Master's Thesis - June 1952
Frank Y. Hayashi	The Synthesis and Characterization of Nitro and Amino Isochromans Master's Thesis - June 1952
Donald K. Burns	Preparation of 6, 8-Dihydroxy Isochroman Master's Thesis - June 1952
Richard L. Rose	The Preparation of Phthalan, Bromo Phthalan, and 6-Hydroxy-phthalan Master's Thesis - Aug. 1954

IN PREPARATION

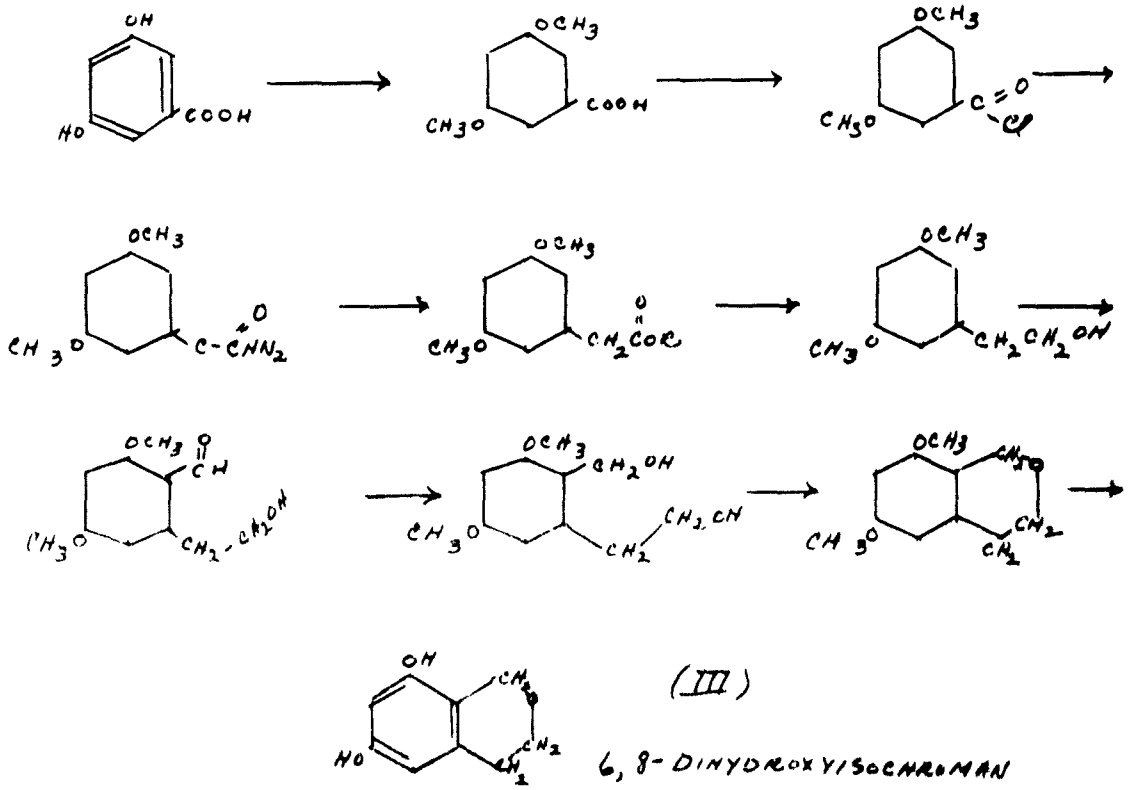
Richard E. Carlson	The Synthesis and Characterization of Bromo-isochromans Master's Thesis

PREVIOUSLY UNREPORTED RESEARCH

During the past year, previous and subsequent to the termination date of the contract, particular efforts have been directed to the syntheses of 6,8-dihydroxyisochroman and a further study of the bromination of isochroman.

Altho several previous attempts that had been made to prepare the dihydroxy compound, none was satisfactory.

The compound was finally prepared by the following series of reactions



(III)

6,8-DIHYDROXYISOCHROMAN

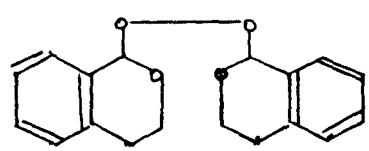
This apparently simple sequence of reactions was not realized without considerable difficulty No compound beyond 3,5-dimethoxybenzoyl chloride had been reported and even up to this point, a reinvestigation of reaction conditions was necessary in order to get adequate quantities of the starting materials.

Satisfactory characterization though derivatives was possible in all cases except 4, 6-dimethoxyl -2- (beta-hydroxyethyl)-benzaldehyde. The final product has not yet been completely characterized since this phase of work has just been completed. However, in the formation of bromo derivatives, it resembles the previously characterized 6 - hydroxyisochroman. Further, the compound forms a stannic chloride adduct, a characteristic reaction of cyclic ethers and typical of isochroman and its derivatives.

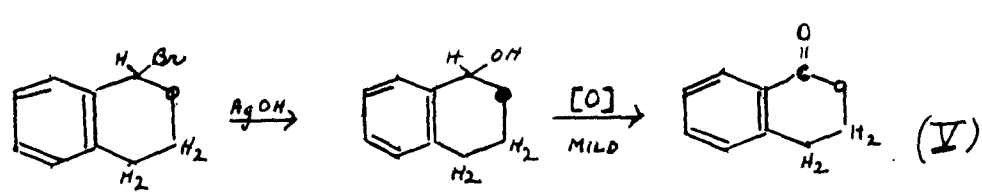
BROMINATION OF ISOCHROMAN

As previously reported isochroman may form two bromo substitution products. Bromine does not enter the aromatic nucleus, but depending upon conditions and the purity of the isochroman, two different products are obtained.

Pure isochroman has been found to auto-peroxidize rapidly on standing, to form a diperoxide (IV)



When directly brominated with radiant energy, either freshly distilled isochroman or peroxide-containing isochroman give largely, if not exclusively, 1-bromoisochroman. The structure of this compound has been established by the following series of reactions

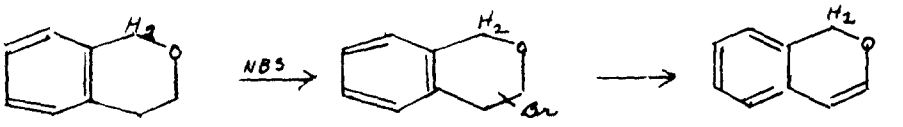


(V)

Since 3, 4 - dihydroisocoumarin (V) has bee prepared previously by an entirely independent method, the identity of 1 - bromoiso-

chroman is substantiated.

When freshly distilled, peroxide-free, isochroman is brominated with N-bromosuccinimide, there is produced along with 1-bromoisochroman, in approximately equal amounts, an unstable 3 or 4-bromoisochroman. This product spontaneously loses HBr to form 3,4-dehydroisochroman. (VI).

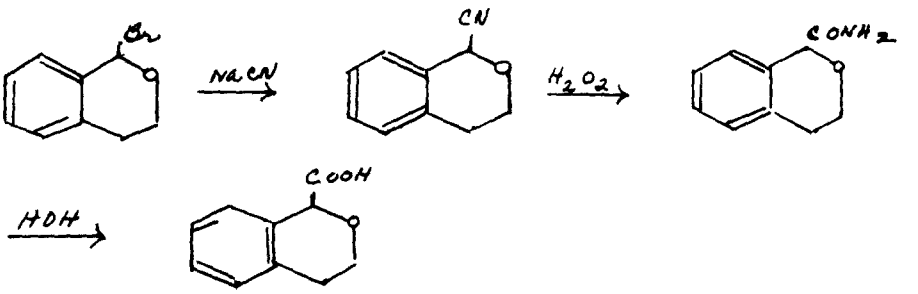


(VI)

Thus far, it has not been possible to determine the structure of the intermediate bromo isochroman because of its great instability. However, work is presently under way to offer a proof of its structure. The best evidence thus far indicates a 4-bromo compound is formed.

The compound, 3,4-dehydroisochroman, has shown the greatest biological activity of the isochroman derivatives prepared thus far. A current program is under way to prepare other derivatives related to it, with possible biological activity.

1-Carboxy-isochroman has been prepared by the following series of reactions:



This compound has been completely characterized, although its biological activity has not been evaluated.